REMARKS

Claims 1-24, 27-31, 33, 36, 38-40, 42, 43 and 45 are currently pending in the application. The claims stand rejected under 35 USC §§103(a) and 112 first and second paragraphs based on a number of positions laid out in detail in the 3/16/06 Office Action. Without conceding to any positions taken by the Examiner, but solely to expedite prosecution of a portion of their invention of particular current interest, Applicant has presented a set of amended claims on pages 2-17 of this paper. Specifically, claims 1, 2, 39 and 43 have been amended, claims 46-61 have been added, and claims 3-31, 33, 36, 38, 40, 42 and 45 remain unchanged. Claims 37, 41 and 44 were cancelled in a previous Amendment by Applicant. Original claims 32, 34 and 35 have been reinstated. Applicant respectfully submits that no new matter is added through the proposed amendment to the claims. Below we address each of the rejections stated in the Office Action as if it were applied to the newly amended claims.

As discussed above, the present Amendment is being made solely to expedite prosecution of the subject matter now claimed, rather than in acquiescence to any positions taken by the Examiner. In fact, Applicant is *not* acquiescing to any of those positions and are submitting their amendments without prejudice to the subsequent prosecution of claims to some or all of the subject matter which might be lost by virtue of this paper.

Amendments to the Claims

Applicant respectfully submits that no new matter is presented with the proposed amendments. The newly added claims are fully supported by the specification and claims, as originally filed. For example, claims 1 and 2, as amended, recite that R_2 is methyl. Support for this amendment can be found, for example, at paragraph [0029] on page 14 of the specification. In addition, amended claims 1 and 2 recite the full original scope of available values for R_9 (See for example original claims 1 and 2 for specific support). Claim 1, as amended, also reinstates variable X, where X is O, NH or CH_2. Support for this language can be found, for example, in original claim 1, paragraph [0014] pp. 8-10, and compounds B2395, ER803734, ER803758 and ER804022 p. 72, 74, 75 and 76. Variable Y in amended claim 1 additionally recites "O" as possible value. Support for this language can be found, for example in original claim 1, paragraph [0059] p. 16 and compounds ER804622 and ER890008 on pages 78 and 85. Claim 39 has been rewritten in dependent form. Claim 43, as amended, includes the compounds of claims 32, 34 and 35, which the present Amendment reinstates. Newly added claims 46-61 find support

throughout the specification. For example, support for claim 46 can be found in original claim 1, paragraphs [0025] and [0026] p. 14 and compounds B2329, ER803604 and ER803734 pp. 71 and 74. Support for claim 47 can be found inter alia in original claim 1, paragraph [0030] p. 14 and compound ER804019 p. 75. Support for claim 48 can be found inter alia in original claim 1, paragraph [0035] p. 15 and compounds on p. 76. Support for claim 49 can be found inter alia in original claim 1, paragraph [0037] p. 15 and compounds on p. 73. Support for claim 50 can be found inter alia in original claim 1, paragraph [0040] p. 15 and compounds on p. 73. Support for claim 51 can be found inter alia in original claim 1, paragraphs [0045] and [0046] p. 15 and compounds ER804745 and ER804746 on p. 79. Support for claim 52 can be found inter alia in original claim 1, paragraphs [0065] and [0066] p. 16 and compounds ER804505 and NF2544 on pp. 77 and 88. Support for claims 53-57 can be found inter alia in original claim 1 and paragraphs [0068]-[0070] p. 16. Support for claim 58 can be found inter alia in original claim 1, paragraph [0072] p. 16 and compounds on p. 77. Support for claim 59 can be found inter alia in original claim 1, paragraph [0073] p. 16 and compounds on p. 77. Support for claim 60 can be found inter alia in original claim 1, paragraphs [0056] p. 15 and [0575]-[0596] pp. 192-198, and compounds NF1226 and NF1227 on p. 87. Support for claim 61 can be found inter alia in original claim 1, paragraphs [0597]-[0614] pp. 199-214, and compounds NF1535 and NF1537 on p. 87.

No new matter is being introduced through these amendments.

The deletion of any claims and any other loss of claimed subject matter is being made solely to expedite prosecution of the subject matter now claimed, rather than in acquiescence to any positions taken by the Examiner. Applicant is submitting the present amendment without prejudice to the subsequent prosecution of claims to some or all of the subject matter which might be lost by virtue of this paper. Applicant explicitly reserves the right to pursue the subject matter of any of the cancelled claims, or some or all of the subject matter which might be lost by virtue of this paper, in Divisional and/or Continuation Applications.

Below we address each of the rejections/objections of record as if it were applied to the newly amended claims.

1. Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-20, 36, 38-40, 42 and 45 under 35 U.S.C. § 103(a) as being unpatentable over Dombrowski *et al.* ("Dombrowski" - *The J. Antibiot.*, **52**(12): 1077-85

(1999)), in view of Patani *et al.* ("Patani" - *Chem. Rev.*, **96**:3147-76 (1996)). The Examiner states that Dombrowski teaches zearalenone-like macrolides wherein R_9 is hydroxyl or methoxy. The Examiner relies on Patani for its teaching that NH_2, Cl and CN are isosteres of methoxy and that Cl, CH_3, H and NH_2 are isosteres of phenolic hydroxy. The Examiner alleges that motivation to combine the cited references is provided by Patani in the teaching that "bioisosterism is considered intuitive and is a common approach used by medicinal chemists in the development of drugs."

Applicant respectfully disagrees with the conclusions of the Examiner.

First, Dombrowski does not teach zearalenone-type macrolides having a hydroxyl at R_9. The only compounds disclosed in that document are show on page 1079. All bear a methoxy at position R_9.

Second, notwithstanding the type of substituent at R_9 described in the Dombrowski compounds, the combination of cited references cannot support a *prima facie* case of obviousness for the reasons stated below.

The legal standard for establishing a *prima facie* case of obviousness requires that three basic criteria be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one skilled in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success in the modification or in the combination; and (3) the prior art reference must teach all the claim limitations. All three requirements must be met to establish a *prima facie* case of obviousness. In addition, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (MPEP 706.02(j)).

The references cited by the Examiner fail *all* three criteria, and therefore cannot be relied on to establish a *prima facie* case of obviousness.

a. There is no motivation to combine

With respect to the motivation to combine the reference teachings, the Examiner relies on the fact that Dombrowski teaches zearalenone-like compounds where R_9 is hydroxy or methoxy. The Examiner further relies on the Patani reference for the teaching of bioisosterism. It is the Examiner's view that bioisosterism is considered intuitive and is a common approach used by medicinal chemists in the development of drugs. According to the Examiner, a skilled person

would have been motivated to replace R_9 with a bioisostere of hydroxyl or methoxy, with the expectation to preserve biological activity.

First, Applicant notes that the Examiner relies on contradictory rationales to support his obviousness rejection on the one hand, and his enablement rejection on the other. Specifically, to support his enablement rejection, the Examiner cites Johnston *et al.* (*J. Med. Chem.*, **13**(5): 941-44 (1970)) and asserts that the reference suggests that deviating from R_9=hydroxy in zearalanone-type compounds destroys biological activity. In the instant obviousness rejection, the Examiner states that the Patani reference provides the motivation to replace R_9 with a bioisostere of hydroxyl or methoxy, with the expectation to preserve biological activity. Applicant submits that the two rejections that the Examiner has formulated are mutually exclusive. Either the Examiner relies on the Johnston reference to support his enablement rejection (in which case the Examiner's characterization of the teaching of the Johnston reference necessarily defeats the Examiner's obviousness rejection over the Dombrowski and Patani references), or the Examiner relies on the Dombrowski and Patani references to support his obviousness rejection (in which case, the Johnston reference cannot teach or suggest what the Examiner states that it does).

Notwithstanding the above-noted contradiction, Applicant addresses below the stated obviousness rejection, as if, contrary to what the Examiner seems to imply, the Johnston reference did not reasonably suggest that deviating from R_9=hydroxy in zearalanone-type compounds destroys *any* biological activity such compounds might be imputed to have.

Applicant respectfully submits that the Examiner's argument is a classic example of impermissible hindsight reconstruction. Indeed, Patani does not teach that replacing *any* given substituent on a compound, such as those disclosed by Dombrowski, with a bioisostere will lead to a derivative with desirable biological properties. Instead, all that Patani teaches is the concept of bioisosterism, and certain examples where the approach was used to draw structure-activity relationships. It is clear from the teachings of Patani that bioisosterism is an *empirical* approach, which can provide SAR trends when applied on a case by case basis. The Patani reference does not support the proposition that bioisosteric substitution can be applied broadly across all possible compound structures with a reasonable expectation that the bioisoteric transformation will lead to the desired biological property. See, for example the paragraph bridging columns 1 and 2 on page 3152:

"The *empirical* approach used to advance the structure-activity relationships with these peptidase inhibitors is useful despite the fact that *a more selective ACE inhibitor was not developed.*" [emphasis added]

Based on these teachings, a skilled artisan would not be motivated to pick out the R_9 position for bioisosteric derivatization, out of the 4 possible -OR sites on the natural compound (F-152) in the expectation that this would yield a zearalenone compound that "inhibits production of a pro-inflammatory and/or immunologic cytokine." Applicant acknowledges that Patani teaches methyl groups as replacements for hydrogen atoms (See section 4 on pages 3152-55). However, Patani does not provide the requisite motivation to pick out the R_2 position for bioisosteric derivatization out of the 16 possible CH sites on the natural compound (F-152) in the expectation that this would yield a zearalenone compound that "inhibits production of a pro-inflammatory and/or immunologic cytokine."

Furthermore, neither Dombrowski nor Patani teaches or suggests that zearalenone-type compounds might have cytokine production inhibitory properties. The only biological activity that the Dombrowski reference suggests for the disclosed compounds is MEK kinase inhibitory activity. Patani *et al.* do not teach nor suggest zearalenone-type compounds, much less their biological activity. Therefore, even if the skilled artisan were motivated to modify Dombrowski's compounds using the teachings of Patani, he or she would have no idea about which position might be appropriate for bioisosteric modification, which bioisostere might be suitable (*e.g.*, NH_2, Cl or CN in place of methoxy), or about the cytokine production inhibitory properties of the resulting compound(s), l*et al*one the reasonable expectation of success that is required to make a *prima facie* case of obviousness.

For these reasons, Applicant respectfully submits that independent claim 1, as amended, is patentable over the disclosure of Dombrowski *et al.* in view of Patani *et al.* Since all pending claims depend ultimately from claim 1, withdrawal of the stated rejection is earnestly requested.

b. There is no reasonable expectation of success

Applicant respectfully submits that the Examiner has not established that there exists the required reasonable expectation of success within the cited references. The teachings, suggestions, and expectation of success must come from the prior art, not applicants' disclosure. See *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants respectfully submit that the

cited references provide no reasonable expectation of success. In fact, the combination of cited references teaches away from the claimed invention. Specifically, the only biological activity that the Dombrowski reference suggests for the disclosed compounds is MEK kinase inhibitory activity. Patani *et al.* do not teach nor suggest zearalenone-type compounds, much less their biological activity. The Federal Circuit has held that "[w]here the prior art does not teach the utility asserted for the claimed compounds, the expectation may not arise, and the motivation would dissipate." See *In re Lalu*, 747 F.2d 703, 707 (Fed. Cir. 1984). In the present case, the references provide no reasonable expectation of success that any of the compounds disclosed therein would be useful as inhibitors of pro-inflammatory and/or immunologic cytokine production, and thus do not establish a *prima facie* case of obviousness. Accordingly, Applicant respectfully submits that independent claim 1, as amended, is patentable over the disclosure of Dombrowski *et al.* in view of Patani *et al.*, and respectfully requests that the Examiner withdraw his rejection of this claim, and dependent claims thereof, under 35 U.S.C. § 103.

c. The references do not teach all the claim limitations

Applicant respectfully submits that neither the Dombrowski nor the Patani reference teaches or suggests zearalenone-type compounds having a methyl at R_2, as recited in currently pending claim 1. In addition, neither cited reference teaches or suggests that zearalenone-type compounds might exhibit the ability to inhibit production of a pro-inflammatory and/or immunologic cytokine. A necessary criterion for establishing a *prima facie* case of obviousness is that the prior art reference or references must teach or suggest all claim limitations. See Manual of Patent Examining Procedure, section 2143.03:

> To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re* Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). 'All words in a claim must be considered in judging the patentability of that claim against the prior art.' *In re* Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

As discussed above, Dombrowski *et al.* fail to teach or suggest zearalenone-type compounds having a methyl at R_2. Patani *et al.* fail to teach or suggest zearalenone-type compounds altogether. Thus, there is nothing in the disclosure of Dombrowski *et al.* and Patani

et al. that would provide one of ordinary skill in the art any motivation to make and use compounds of the invention where R_2 is methyl. In addition, there is nothing in the disclosure of the cited references to teach or suggest that zearalenone-type compounds have the ability to inhibit production of a pro-inflammatory and/or immunologic cytokine. As such, claim 1, as amended, and claims that depend from it, are not rendered obvious by the disclosure of Dombrowski *et al.* in view of Patani *et al.*

Any one of the remarks a-c above *alone* defeats the Examiner's rejection under 35 U.S.C. § 103(a). In addition, the following remarks further support Applicant's position that the Examiner failed to establish a *prima facie* case of obviousness.

1. Evidence of unexpected results thwarts the presumption of obviousness

The claims are directed to compositions comprising compounds of the invention where R_2 is methyl, and methods for using them. As detailed in the enclosed Declaration from inventor John (Yuan) Wang and accompanying Exhibit 4, the selection of R_2 = methyl provides superior stability properties due to the unusual and unexpected ability of a methyl group at R_2 to stabilize the enone at C5-C6. Exhibit 4 sets out a comparison between the stability of compounds of the present invention with a compound cited in the prior art (F-152). The prior art compound F-152 was found to be metabolically unstable as the enone C5-C6 quickly isomerizes in mouse plasma (as illustrated in Graph 1 of Exhibit 4). However, Applicant recognized and demonstrated that the addition of a methyl group at position R_2 stabilizes the enone at C5-C6 and significantly improves the plasma level of compounds over time in mouse (as illustrated in Graph 2 of Exhibit 4). This stabilization is observed in compounds recited in the present composition and method claims, as further evidenced by the data set out in Graph 3 of Exhibit 4.

Dombrowski and Patani fail to suggest any reason for selecting R_2 = methyl as result effective variable. Indeed, neither reference teaches or suggests zearalenone-type compounds substituted at position R_2. The Examiner's obviousness rejection relies solely on the structural similarity of the art and Applicant's compounds, and the expectation of obtaining similar properties for structurally similar compounds. As the CCPA established *In re* Papesch, structural similarity is not sufficient to support a finding of obviousness in the face of unexpected or superior properties among similar compounds. *In re* Papesch, 315 F.2d at 382, 137 USPQ at 44. Papesch claimed certain trialkyl copounds, in which the alkyl groups contained "more than one

or less than five carbon atoms." Id. The USPTO rejected Papesch's claims based on a prior art reference disclosing a trimethyl group, reasoning that the prior art compound's structural similarity made the claimed compounds obvious. In response, Papesch filed a declaration reporting the results of testing that showed a triethyl compound of the invention had anti-inflammatory activity while the trimethyl did not. The Board sustained the examiner's rejection, giving no weight to the evidence submitted in the declaration. In finding the declaration's evidentiary showing persuasive of the claimed invention's patentability, the CCPA reversed the Board and stated:

> "[W]e think that [the Board's rejection] rests on one fundamental error of law, namely, the failure ot take into consideration the biological or pharmaceutical property of the compounds as anti-inflammatory agents on the ground that to chemists the structure of the compounds would be so obvious as to be beyond doubt, and that a showing of such property is to be used only to resolve doubt.
>
> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing... And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous."

Here, Applicant provided evidence in the form of a declaration that the presence of a methyl group at R_2 imparts beneficial stability properties to the compounds. The recognition by Applicant, unsuggested in the cited art, that the presence of a methyl group at R_2 enhances plasma stability of the compounds recited in the claims is the touchstone of unobviousness. Thus, the combination of cited art cannot render the pending claims obvious. It is therefore respectfully requested that the rejection be reconsidered and withdrawn.

2. The cited art does not disclose any method for making structurally similar compounds

It is well established that, where no known or obvious method exists for making a compound, merely naming or suggesting a compound will not constitute a description of the

compound and will not place it in possession of the public. See *In re* Hoeksama, 399 F.2d at 273, 158 USPQ at 600. The court *In re* Hoeksama held:

> "[U]pon careful consideration it is our view that if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not legally be concluded that the compound itself is in possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds."

In this case, the Dombrowski reference teaches naturally-occurring zearalenone-type compounds isolated from fermentation of fungi cultures. The fermentation techniques described in Dombrowski do not allow the preparation of zearalenone-type compounds having a non-naturally occurring substitution pattern (*e.g.*, where R_2 is methyl). Thus, Dombrowski does not teach synthetic approaches that would allow the *de novo* synthesis of zearalenone-type compounds where R_2 is methyl, such as those recited in the claimed composition and method claims. Patani *et al.* do not teach nor suggest zearalenone-type compounds, much less methods for making them. Thus, the combination of cited references cannot render obvious the compounds recited in the present claims. It follows that the cited references cannot support a *prima facie* case of obviousness of claim 1.

Since independent claim 1 as currently amended is not rendered obvious in light of Dombrowski *et al.* in view of Patani *et al.*, and since all pending claims depend ultimately from claim 1, Applicant respectfully requests that the outstanding rejection under 35 U.S.C. §103 be withdrawn.

2. Rejections Under 35 U.S.C. § 112, First Paragraph

Rejections of Claims 1-24, 27-31, 33, 36, 38-40, 42, 43 and 45 under 35 U.S.C. § 112, First Paragraph for Lack of Written Description

The Examiner has rejected claims 1-24, 27-31, 33, 36, 38-40, 42, 43 and 45 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The

Examiner rejected the amendment deleting "hydroxyl, protected hydroxyl, OR_{12}" from the definition of R_9 in claim 1, and alleges that the resulting definition is not supported by the originally filed application.

Without conceding the correctness of the Examiner's position, but solely to expedite prosecution of a portion of their invention of particular current interest, Applicant has reinstated the original definition of R_9. Therefore, the stated rejection is now moot.

In fact, Applicant respectfully submits that the rejection under § 112, First Paragraph is improper. The Examiner appears to base his rejection on *Ex parte Batchelder*, 131 USPQ 38 (1960), which is no longer valid authority. *Ex parte Batchelder* stood for the proposition that a claim amendment that eliminated one or more members from a Markush group was new matter if there was no support in the specification as originally filed for the new grouping. That case was overruled in 1977 by the U.S. Court of Customs and Patent Appeals. See *In re Driscoll*, 562 F.2d 1245 (CCPA 1977); also *In re Johnson and Farnham*, 194 USPQ 187 (CCPA 1977). The Applicant, Driscoll, had amended the appealed claim (claim 13) to recite that variable "R is alkylsulfonyl (C_1-C_6)," when in the originally filed application, R was defined using a Markush group of 14 members. Claim 13 was rejected under 35 U.S.C. § 102 as anticipated by Belgian patent No. 743,615, the effective reference date of which is June 23, 1970. The examiner took the position that the Applicant was not entitled to the benefit of a filing date prior to the reference date because nowhere in the Applicant's earlier filed applications was there a written description of the subject matter of claim 13 in "full, clear, and exact terms," as required by 35 U.S.C. § 112. The Board of Appeals affirmed the Examiner's rejection. However, the CCPA in this case reversed the rejection under 35 U.S.C. § 112 and held:

> "A comparison of the appealed claim [claim 13] with the class of compounds disclosed in S.N. 782,756 reveals that the only difference therebetween lies in the definition of the substituent designated by R. In the appealed claim, R is simply alkylsulfonyl (C_1-C_6), whereas in the earlier application, R corresponds to a Markush group of fourteen variable substituents (the R group), one of which is alkylsulfonyl (C_1-C_6)."

"We thus agree with appellant that a skilled artisan would recognize from the disclosure of S.N.782,756 fourteen distinct classes of compounds, each class having a single member of the R group at the 5-position of the thiadiazole moiety and variable substituent groups on the urea moiety. This being the case, it follows that S.N.782,756 describes the subject matter of claim 13 inasmuch as one of the fourteen classes of compounds is the 5-alkylsulfonyl-1,3,4-thiadiazole ureas defined therein."

Accordingly, the Examiner erred in rejecting claims 1-24, 27-31, 33, 36, 38-40, 42, 43 and 45 under 35 U.S.C. § 112, first paragraph on grounds that the definition of variable R_9 had been amended to remove members from the original Markush group. As the U.S. Court of Customs and Patent Appeals made clear *In re* Driscoll, Applicant's deletion of one or more members of a Markush group cannot be held to lack "written description" under 35 U.S.C. § 112, ¶ 1. Withdrawal of the rejection of record under 35 U.S.C. § 112, First Paragraph for Lack of Written Description is earnestly requested.

Rejections of Claims 1-24, 27-31, 33, 36, 38-40, 42, 43 and 45 under 35 U.S.C. § 112, First Paragraph for Lack of Enablement

Pending claims 1-24, 27-31, 33, 36, 38-40, 42, 43 and 45 stand rejected for lack of enablement. In particular, the Examiner takes the position that the specification does not reasonably provide enablement for R_9 being other than hydroxy. The Examiner acknowledges that the specification provides many examples and methods of making zearalenone-like macrolides wherein R_9 is a number of substituents other than hydroxy, but alleges that data showing that these compounds exhibit biological activity does not exist. The Examiner further points to Johnston *et al.* (*J. Med. Chem.*, **13**(5): 941-44 (1970)) and asserts that the reference suggests that deviating from R_9=hydroxy in zearalanone-type compounds destroys biological activity. Relying on the *Wands* factors, the Examiner asserts that a person of ordinary skill in the art would be subject to undue experimentation in order to make and use the claimed invention. This rejection is respectfully traversed; reconsideration and withdrawal is requested.

The Examiner has listed the non-limiting *Wands* enablement factors and has addressed these factors as they relate to the claimed invention. *See In re Wands*, 858 F.2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988). These are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of one of ordinary skill in the art;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The existence of working examples; and
8. The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Applicant responds to the Examiner's characterization of these factors as they relate to the claimed invention in the order presented by the Examiner.

(1) The breadth of the claims:

The Examiner contends that the claims are broad due to the high number of compounds they embody. Applicant notes that the claimed pharmaceutical compositions and methods embody compounds where R_2 is methyl. The specification, as filed, provides numerous examples of compounds of this class, as well as synthetic methods for making them and assessing the compounds' biological activity. The compounds and synthetic methods disclosed in the application cover a significant scope in structural diversity (*i.e.*, variables R_1, R_3-R_{10}, X, Y, Z). Thus, the breath of the claims is reasonably commensurate with the amount of direction and guidance provided in the specification.

(2 and 5) The nature of the invention and the level of predictability in the art:

The Examiner contends that the claimed invention is physiological in nature as it is directed to pharmaceutical compositions and methods of treatment, an art allegedly highly unpredictable. Applicant respectfully disagrees. The specification provides ample guidance about the correlation between NF-κB inhibitory activity and the claimed methods of treatment (See, for example, paragraphs [0134]-[0139] of the specification. In addition, methods of assessing the compounds' biological activity are described in the application, as filed (See, for example, paragraphs [1321]-[1332]). Thus, far from being an unpredictable field, as the Examiner asserts,

specific methods of assessing NF-κB inhibitory activity are well known to those of ordinary skill in the art. Using known methods of assessing NF-κB inhibitory activity, and armed with the synthetic guidance provided in the specification, one of ordinary skill in the art is enabled to practice the claimed invention.

(3) The state of the prior art:

The Examiner asserts that prior art suggests that deviating from R_9=OH has dramatic effects on the biological activity of zearalenone derivatives, citing Johnston *et al.* (*J. Med. Chem.*, **13**(5): 941-44 (1970)). Applicant submits that the Johnston *et al.* reference cannot meaningfully provide any insight as to the state of the prior art of the presently claimed invention. Specifically, the Johnston *et al.* reference reports on the *estrogenic activity* of certain zearalanone compounds. Thus, any structure/activity conclusions reported in that reference having to do with structural modifications at R_9 are not relevant to the claimed invention, since *estrogenic activity* was under study in the Johnston *et al.* reference not NF-κB inhibitory activity, or inhibition of pro-inflammatory and/or immunologic cytokine production. While R_9=OH may be required in the compounds of the Johnston *et al.* reference for estrogenic activity, no conclusions can be drawn for NF-κB inhibitory activity, or any other activities unrelated to estrogenic activity for that matter. Thus, unlike what the Examiner asserts, the cited reference does not suggest anything with respect to the biological activity of the compounds of the invention.

(4) The level of one of ordinary skill:

Applicant agrees with the Examiner that the skill level of one of ordinary skill in the art would be high, most likely at the Ph.D. level.

(6 and 7) The amount of direction provided by the inventor and the existence of working examples:

The Examiner contends that the specification shows how to make the inventive compounds, but fails to demonstrate that they maintain biological activity. The Examiner further states that the specification contains no working examples demonstrating the biological activity of the inventive compounds.

Applicant submits that the specification does in fact provide adequate enablement support. The specification describes that inventive compounds have the ability to inhibit NF-κB and pro-inflammatory and/or immunologic cytokine production. See, for example, paragraphs [0007] p. 3 and [0131] p. 42 of the application. The specification further details compound preparation protocols prior to submission for biological testing (See paragraph [0224] p. 91 of the specification). The enclosed Declaration from inventor John (Yuan) Wang provides a sample of the biological data that was collected *in vitro* and *in vivo*. As is readily apparent from the data, compounds of the invention do have in fact NF-κB inhibitory activity, and anti-inflammatory activity.

Applicant additionally submits that, in the context of assessing the adequacy of the description for purposes of the enablement requirement, the description provided must be read from the point of view of one skilled in the art. *See In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996). Those of ordinary skill in the art are well versed in appropriate assays to assess the biological activity (*e.g.*, NF-κB inhibitory activity) of compounds falling within the scope of the genus of claim 1. Furthermore, armed with the synthetic guidance provided in the specification, those of ordinary skill in the art are capable of identifying those functionalization reactions that are appropriate for any given compound within the scope of the genus of claim 1. It is well established that the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and is available to the public. *In re Buchner* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Thus, when read from the point of view of one of ordinary skill in the art (*i.e.*, with commensurate knowledge of NF-κB inhibitory activity assays and functionalization reactions), Applicant submits that the guidance required by the enablement requirement is provided in the disclosure of novel methods of making and using pharmaceutical compositions comprising compounds of the invention. Thus, Applicant submits that one of ordinary skill in the art is in fact enabled to practice the claimed invention based on the teaching of the present disclosure.

(8) The quantify of experimentation needed to make or use the invention based on the content of the disclosure

The Examiner contends that as a result of the breadth of the claims, the contradictory art, the limited guidance from the specification and the high degree of skill required to practice the

invention, the quantity of experimentation needed to make and/or use the invention would be high.

For the reasons presented above in the Working examples section, Applicant disagrees. As indicated, the description provided must be read from the point of view of one skilled in the art. *See In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996). Those of ordinary skill in the art are well versed in appropriate assays to assess the biological activity (*e.g.*, NF-κB inhibitory activity) of compounds falling within the scope of the genus of claim 1. Furthermore, armed with the synthetic guidance provided in the specification, those of ordinary skill in the art are capable of identifying those functionalization reactions that are appropriate for any given compound within the scope of the genus of claim 1.

Disclosure of working examples of techniques known to those skilled in the art is not necessary. *See, e.g., Manual of Patent Examination Procedure*, ch. 2164.05(a), discussing this issue in the context of enablement. *See also In re Buchner* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and is available to the public.")

Furthermore, Applicant disagrees that the prior art identified by the Examiner is contradictory. In fact, Applicant submits that the Johnston *et al.* reference cannot meaningfully provide any insight as to the state of the prior art of the presently claimed invention. As discussed in the State of the Art section above, the Johnston reference cited by the Examiner relates to *estrogenic activity* of zearalanone-type compounds. Thus, any structure/activity trends reported in that reference have no relevance to the claimed invention, since Johnston discusses *estrogenic activity* not NF-κB activity, or inhibition of pro-inflammatory and/or immunologic cytokine production.

The quantity of experimentation needed to make or use the invention, based on the content of the disclosure, is neither excessive nor outside the skill set of one skilled in the art. As stated in *Wands*, "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" *Wands* at 1404 (emphasis added). As discussed above, one of ordinary skill in the art is well versed in both assays to assess the claimed biological activity, and in appropriate functionalization reactions to

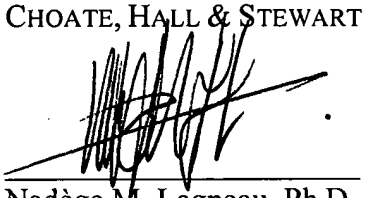
make the compounds for use in the claimed invention. The fact that the practitioner may need to perform routine experiments to determine which assays and/or functionalization reactions to utilize when practicing the claimed invention does not mean that the art is highly unpredictable. As such, a rejection of the instant claims based on lack of enablement is improper.

CONCLUSION

Applicant thanks the Examiner for his/her time and consideration. If a telephone conversation would help clarify any issues, or help expedite prosecution of this case, Applicant invites the Examiner to contact the undersigned at (617) 248-5150.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those which may otherwise be provided for in documents accompanying this paper. However, in the event that any additional fees are required for consideration of this paper (including fees for net addition of claims), these fees are authorized to be charged to our Deposit Account No. 03-1721.

Respectfully submitted,
CHOATE, HALL & STEWART LLP



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Date: August 16, 2006

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